

REMARKS

An Office Action was mailed in the above-captioned application on October 6, 2006. In such Office Action claims 1-3, 5, and 7-12 were pending. Claims 1-3, 5, and 7-12 were rejected. This Amendment and Remarks document is submitted in response to said Office Action.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-3, 5, and 8-12 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art the inventors, at the time the application was filed, had possession of the claimed invention. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003).

Specifically, the rejection states that the specification teaches only a single mouse strain that is resistant to collagen-induced arthritis and does not provide any description or reduction to practice of other rodents resistant to collagen-induced arthritis. Applicant respectfully traverses this rejection. Solely in the interest of expediting prosecution, Applicant has amended claims 1-3, 5, 7 and 8 to refer to a transgenic mouse. Applicant reserves the right to pursue cancelled subject matter in a continuing application.

Applicant submits that the claims as amended satisfy the written description requirement. It is well known to persons having ordinary skill in the art, which mouse strains are resistant to collagen-induced arthritis (CIA), as CIA resistance is known to be associated with the genotype at the comprehensively described MHC locus. For example, in the present specification, a DBA/1 (H-2^q) mouse is used as a CIA susceptible control in the Examples. In support of this, enclosed is a publication, Wooley *et al.*, (1981) *J. Exp. Med.* 154: 688-700, which teaches the “incidence of type II collagen arthritis and maps the susceptibility to the disease within the region of the MHC” in mice and describes the mapping of CIA susceptibility to the H-2 complex in the I^q region (see, in particular, page 694 line 11 to page 695 line 11). CIA susceptibility has since also been mapped to include the H-2^f haplotype, and this is well known (see for example, the enclosed publication Hom *et al.* (1992) *Clin Immunol Immunopathol.* 62: 56-65 at page 56

column 2 lines 2 to 6, which describes, at page 56 column 2 lines 3-5, that the “ susceptibility to CIA in mice is H-2 restricted and limited to strains of the H-2^q or H-2^r haplotype”). The skilled artisan, therefore, would be able to understand what is encompassed by the description of a mouse resistant to collagen-induced arthritis in the present specification. The human FcγRIIa transgenic mouse is of a C57/B16 x SJL background, which has a MHC subtype of H-2^{b/s} (see, e.g., page 18 lines 10 to 12), which is, of course, why it was so surprising that the presence of the FcγRIIa transgene rendered the mouse susceptible to CIA.

For the foregoing reasons, Applicant request reconsideration of the rejection under 35 U.S.C. § 112, first paragraph as lacking written description.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-3, 5 and 7-12 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art the inventors, at the time the application was filed, had possession of the claimed invention.

The first paragraph of § 112 requires that a patent application be written so as to “ enable any person skilled in the art to which it pertains . . . to make and use the same.” A specification is presumed to be enabling absent “ a reason to doubt the objective truth of the statements contained therein.” *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification “ may be enabling even though some experimentation is necessary,” *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not “ undue experimentation.” *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification “ provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Specifically, the rejection states that the claims read on a transgenic rodent that is susceptible to any autoimmune disease, the use of any strain of rodent that is resistant to CIA to produce the transgenic rodent as claimed, and methods of screening compounds by assessing any type of cell derived from the transgenic rodent as claimed to determine if the compound reduces aberrant immune activity.

Applicant does not acquiesce in this rejection; however, solely in the interest of expediting prosecution, Applicant has amended claims 1-3, 5, 7 and 8 to refer to a transgenic mouse. Thus, the claims can no longer be regarded as reading onto the “use of any . . . rodent that is resistant to collagen-induced arthritis” (i.e. the amended claims are limited to mice).

The amended claims recite that the mouse is from a strain that is resistant to collagen-induced arthritis. As noted above, strains resistant (and susceptible) to collagen-induced arthritis are known to the skilled artisan. Moreover, it is well within the routine skill of persons having ordinary skill in the art to test whether a mouse strain with an unknown genetic background is resistant to CIA. The above-mentioned Wooley et al. (1981) reference, teaches a method of determining susceptibility to collagen-induced arthritis (see page 689, lines 7 to 35).

After testing whether a mouse strain is resistant to CIA, it is and then routine to transgenically modify a mouse found to be resistant to CIA to express FcγRIIa. The rejection indicates that the possible variations in the phenotype of transgenic mice, and the unpredictability in the field of mouse transgenics, that undue experimentation would be required to practice the claimed invention; however, Applicant submits that the production of transgenic mice comprising and expressing the human FcγRIIa receptor is routine and does not involve undue experimentation. McKenzie, et al., (1999) *J. Immunol.* 162:4311-18, of record, provides detailed procedures regarding the production of transgenic mice comprising and expressing the human FcγRIIa receptor. At least four transgenic mice expressing the human FcγRIIa receptor were generated, and one of these was chosen for further study (McKenzie, et al., p. 4312, second column; page 4314, second column to page 4315). Given this disclosure, Applicant submits that one of ordinary skill in the art would be able to produce a transgenic mouse comprising and expressing the human FcγRIIa receptor without undue experimentation.

The rejection alleges that the specification does not provide sufficient guidance or support “for generating a phenotype of enhanced susceptibility to any immune disease . . . other than collagen-induced arthritis” (page 10 of the Office Action). Applicant respectfully points out that the present specification does, in fact, provide evidence that the transgenic mice of the invention, in addition to showing susceptibility to CIA, spontaneously develop arthritis in the absence of collagen immunization and show symptoms of systemic lupus erythematosus (SLE) (see, in particular, Examples 2 and 3). Solely in the interest of expediting prosecution, however, the reference to “autoimmune disease” in step (a) of each of claims 1-3 has been amended to

recite “ autoimmune disease caused by aberrant immune complex formation, aberrant immune complex clearance or immune complex induced inflammation”. Support for this amendment can be found at, for example, page 10 lines 25 to 38 of the present specification. Applicant reserves the right to pursue cancelled subject matter in a continuing application.

Regarding claim 3, the rejection has alleged on page 6 and page 11 of the Office Action that Claim 3 reads onto methods of screening compounds by assessing “any type of cell derived from the transgenic rodent as claimed”. Applicant respectfully points out that Claim 3 is not directed to “any” cell, but rather clearly limits the cell to “ a non-human cell *expressing* human FcγRIIIa receptor.” Solely in the interest of expediting prosecution, however, claim 3 has been amended to recite that the cell is selected from the group consisting of platelets, neutrophils and macrophages. Support for such an amendment can be found in the present specification at page 18 lines 12-14. We note that 0, describes that the expressed human FcγRIIIa was found in megakaryocytes, leukocytes (of which *neutrophils* are well known to be the major cell type, see the enclosed Table 3-1 of Kuby (1994), *Immunology*, at page 48), macrophages and platelets (see page 4315, column 2 lines 15 to 40).

For the foregoing reasons, Applicant requests reconsideration of the rejection under 35 U.S.C. § 112, first paragraph as lacking enablement.

The Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 2, 5 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over McKenzie, et al., (1999), *J. Immunol.* 162:4311-4318. The Examiner bears the burden of establishing a prima facie case of obviousness (Section 103). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Specifically, the rejection states that McKenzie, et al. suggests using the FcγRIIIa receptor transgenic mouse to test therapeutic modalities. Applicant respectfully traverses this rejection.

McKenzie, et al., is entirely directed towards the elucidation of the role of FcγRIIa in *thrombocytopenia* in the presence or absence of the FcR γ chain. Accordingly, the results and conclusions of McKenzie, et al., do not in any way suggest that the mouse can *spontaneously* develop a *systemic* autoimmune disease “caused by aberrant immune complex formation, aberrant immune complex clearance or immune complex induced inflammation” (e.g. rheumatoid arthritis and SLE) and, therefore, be useful for screening for compounds able to suppress such a disease, as described in the present application. Specifically, McKenzie, et al., teaches that, compared to its wild-type litter mates, the FcγRIIa transgenic mouse is susceptible to enhanced immune thrombocytopenia following intravenous or intraperitoneal administration of *exogenous* rat anti-mouse platelet antibodies, using a previously established model of thrombocytopenia (see page 4313, column 2 lines 20 to 24), wherein the exogenous anti-platelet antibodies bind specifically to antigen on the platelet surface. The cited document indicates on page 4316, column 1 lines 7 to 11, that the rat anti-mouse platelet antibody (i.e. 4A5 Ab) used to induce the thrombocytopenia was not capable of aggregating platelets derived from the transgenic mouse *in vivo*. Therefore, the FcγRIIa transgenic mouse of McKenzie, et al., is *only* described in the context of its use as a model of thrombocytopenia characterized by the removal of platelets due to *normal* immune complex clearance of a single type of immune complex which is known and defined, the formation of which is *dependent* upon the administration of *exogenous* antibodies directed against a single specific antigen. Further, the only analysis of the immune response in the transgenic mouse taught in McKenzie, et al., is that of platelet counts. There is, accordingly, no attempt to further characterize the immune response of the mouse, and additionally, no mention or suggestion that the mouse may be *spontaneously* susceptible to systemic autoimmune disease or *aberrant* immune complex formation, *aberrant* immune complex clearance or immune complex-induced inflammation. While the authors conclude that “the human Fc receptor FcγRIIa plays a significant role in the immune clearance of platelets *in vivo*” (see lines 13 to 14 of the abstract), they clearly make that conclusion on the basis of platelet counts *alone* following *administration of exogenous anti-platelet antibodies*.

Further, there is no suggestion in McKenzie, et al., that these mice can spontaneously develop *symptoms* of systemic autoimmune disease “caused by aberrant immune complex formation, aberrant immune complex clearance or immune complex induced inflammation”, or

that the mouse should be susceptible to CIA, which is also caused by aberrant immune complex formation, aberrant immune complex clearance or immune complex induced inflammation.

In this regard, it is to be noted that while McKenzie, et al., may suggest that a transgenic mouse could be useful to screen therapeutic modalities in thrombocytopenia, such as heparin-induced thrombocytopenia with thrombosis, there is no mention or suggestion in McKenzie, et al., that the mouse is useful for screening for any other purpose, including screening for compounds able to suppress diseases associated with aberrant immune complex formation, aberrant immune complex clearance or immune complex induced inflammation, which is the subject of the present claims.

The disease symptoms described, for example, in Examples 2, 3 and 4, are multifactorial and derived from the formation of *aberrant* immune complexes associated with the *in vivo* production of *endogenous* antibodies directed at a *variety* of self antigens, and subsequent *aberrant* immune-complex clearance and immune complex induced inflammation. For example, Example 2 reports results from a spontaneous arthritis (SA) mouse model. Symptoms include swelling and reddening of the footpads and stiffening of the digits, knees and ankles, and inflammation with synovium hyperplasia and infiltration by polymorphonuclear cells. Example 3 reports an assessment of systemic lupus erythematosus (SLE). SLE is an autoimmune disease characterized by the development of antinuclear antibodies (ANA), especially against DNA, development of antibodies to red and white blood cell surface antigens, leading to anemia, thrombocytopenia, leukopenia, endothelial cell damage and vasculitis. Example 4 reports results from a collagen-induced arthritis (CIA) mouse model. Symptoms include synovial inflammation, articular erosion, and the development of pannus in the joint.

It is submitted that the symptoms associated with these aberrant activities are quite distinct from the immune clearance observed in the thrombocytopenia model of McKenzie, et al.

Reconsideration of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-1970, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-1970.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: /Darla G. Yoerg/

Darla G. Yoerg
Registration No. 48,053
1560 Broadway, Suite 1200
Denver, Colorado 80202-5141
(303) 863-9700

Date: February 22, 2007